Partially Protected Polyamines

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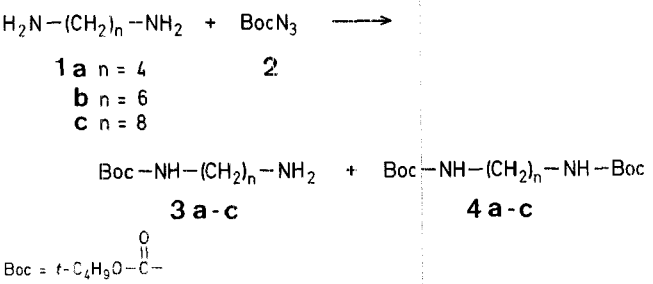
Naturally occurring polyamines and their derivatives are biologically important. They are known to have high affinity for nucleic acids, and to exhibit a variety of effects on nucleic acid biosynthesis and metabolism[1].

Frequently the synthesis of polyamines necessitates the use of protecting groups[2]. The use of such protecting groups is also warranted in many cases where selective reaction at specific amino groups in polyamines is required[3,4]. The *t*-butyloxycarbonyl (Boc) group is a convenient and widely used protective group for amines, which is easily removed under mild acid conditions[5]. Several methods exist for the attachment of the Boc-group to amines, and the one most commonly used employs *t*-butyloxycarbonyl azide (**2**; $BocN_3$) as the reagent.

We now report a fast and simple procedure for the preparation of polyamines protected at some or all of their primary amino groups[6].



$H_2N-(CH_2)_n-NH_2$ + $BocN_3$ ⟶

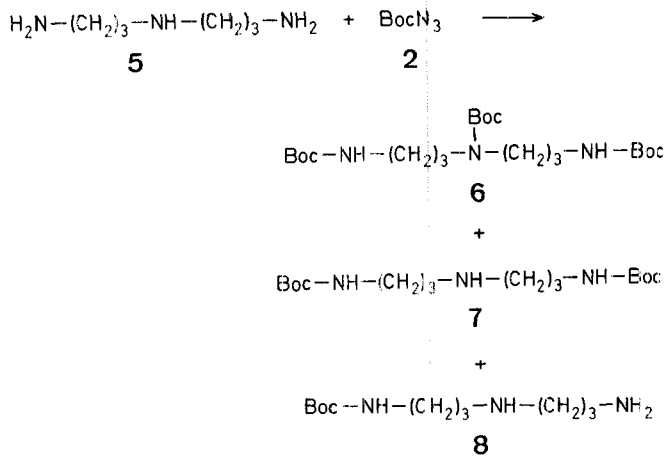
1a n = 4 **2**
b n = 6
c n = 8

$Boc-NH-(CH_2)_n-NH_2$ + $Boc-NH-(CH_2)_n-NH-Boc$

3a-c **4a-c**

Boc = $t\text{-}C_4H_9O-\overset{O}{\overset{\|}{C}}-$

The treatment of α,ω-diaminoalkanes **1** with **2** in dimethyl sulfoxide, or in a mixture of dioxan and water for 1 h resulted in the formation of mixtures of the mono- and diprotected diamines, **3** and **4**, the former solvent giving the highest yield of monoprotected amine **3**. The products were separated from the reaction mixture by extraction at pH 5 (di-Boc-derivatives; **4a-c**) and at pH 12 (mono-Boc-derivatives; **3a-c**). The monoprotected diamines (**3a-c**), which were obtained as oils, could be converted to their crystalline hydrochlorides by a procedure which did not cause significant deprotection. Similarly treatment of 1,7-diamino-4-azaheptane (**5**) with **2** in dimethyl sulfoxide afforded a mixture of the tri-, di- and monoprotected amines (**6, 7, 8**), which were separated by extraction at different pH values.



$H_2N-(CH_2)_3-NH-(CH_2)_3-NH_2$ + $BocN_3$ ⟶

5 **2**

$Boc-NH-(CH_2)_3-\overset{Boc}{\overset{|}{N}}-(CH_2)_3-NH-Boc$

6

+

$Boc-NH-(CH_2)_3-NH-(CH_2)_3-NH-Boc$

7

+

$Boc-NH-(CH_2)_3-NH-(CH_2)_3-NH_2$

8

The sites of the protecting groups in compounds **7** and **8** were easily verified (^{1}H-N.M.R.) by determining the ratio between the protons α to amido groups (at 3.3–3.1 ppm) and to amino groups (at 2.9–2.6 ppm).

We were not able to obtain compound **6** in crystalline form although it was pure by T.L.C. in two different solvent mixtures. The compound had satisfactory ^{1}H-N.M.R. and mass spectra.

The reactions were conveniently followed by T.L.C. (silica gel 60, Merck, eluted in 2-butanol:formic acid:water, 15:3:2). In order to visualize the products, the T.L.C. plates were sprayed with *t*-butyl hy-

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Table. Compounds **3a, c** and **4a, c** prepared in Dimethyl Sulfoxide

Product No.	n	Yield [%] based on **1**	Yield [%] based on **2**	m.p. [°C] (solvent)	Molecular formula[a]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
3a	4	44	44	155–156° (ethyl acetate/hexane)	$C_9H_{20}N_2O_2 \cdot HCl$ (224.7)	1.48 (br s, 20 H); 2.7–2.8 (m, 2 H); 3.0–3.3 (m, 2 H); 5.0–5.3 (br, 1 H)
3c	8	28	20	162–163° (ethyl acetate/hexane)	$C_{13}H_{28}N_2O_2 \cdot HCl$ (280.8)	1.30 (br s, 10 H); 1.44 (br s, 13 H); 2.6–2.7 (br s, 2 H); 3.1–3.3 (m, 2 H); 4.8–5.1 (br, 1 H)
4a[b]	4	25	50	134–135° (ethyl acetate)	$C_{14}H_{28}N_2O_4$ (288.4)	1.42 (br s, 2 H); 1.44 (br s, 22 H); 3.0–3.3 (m, 4 H); 4.8–5.0 (br, 2 H)
4c[b]	8	44	66	106–107° (ethyl acetate)	$C_{18}H_{36}N_2O_4$ (344.5)	1.31 (br s, 8 H); 1.44 (s, 22 H); 3.0–3.2 (m, 4 H); 4.4–4.7 (br, 2 H)

[a] Satisfactory microanalyses obtained: C ±0.21, H ±0.19, N ±0.14, Cl ±0.13.
[b] Ratio of **2** : **1** (n = 8) = 1.5 : 1.

pochlorite in cyclohexane [prepared from *t*-butyl alcohol (16 g) in cyclohexane (800 ml)], dried at 100°C for 2 min, and subsequently sprayed with 0.1% (w/v) *o*-toluidine in 1 molar acetic acid, containing 0.5% (w/v) potassium iodide.

Reaction of 1,6-Diaminohexane (1b) with 2; Typical Procedure:
Boc azide (**2**; 71.6 g, 0.5 mol) in ether (130 ml) is added dropwise to a stirred solution of 1,6-diaminohexane (**1b**; 58.1 g, 0.5 mol) in dimethyl sulfoxide (250 ml) and the temperature is kept at 25°C with Dry Ice/acetone cooling. After the addition is completed (30 min), stirring is continued at room temperature for 1 h, whereupon water (500 ml) and ether (750 ml) are added. After vigorous stirring for a few min, the ether phase is isolated, extracted with aqueous hydrochloric acid (250 ml, pH 4.7), washed with water (200 ml), dried with anhydrous magnesium sulfate, and concentrated in vacuo to give **4b**; yield: 46.5 g (59% based on **2**, 30% based on **1b**); m.p. 101–102°C (from ethyl acetate).

$C_{16}H_{32}N_2O_4$ (316.4)	calc.	C 60.73	H 10.19	N 8.85	
	found	60.80	10.29	8.88	

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.48 (br s, 26 H); 3.1–3.3 (m, 4 H); 4.8–5.0 ppm (br s, 2 H).

The combined aqueous extracts from above are made alkaline (pH 12) with 6 normal sodium hydroxide and extracted with ether (4 × 750 ml). The ether phase is washed with concentrated aqueous sodium chloride (2000 ml), concentrated to 300 ml by evaporation, and mixed with water (200 ml). The pH of the vigorously stirred mixture is adjusted to 5.3 with 6 normal hydrochloric acid, whereupon the ether is evaporated in vacuo, and the residual aqueous solution lyophilized to give the hydrochloride of **3b**. Recrystallization from ethyl acetate : ethanol (4 : 3) gives **3b** · HCl as white crystals; yield: 48 g (38% based on **2**, 38% based on **1b**); m.p. 153–154°C.

$C_{11}H_{24}N_2O_2 \cdot HCl$ (252.8)	calc.	C 52.27	H 9.97	N 11.08	Cl 14.02
	found	52.27	10.06	11.02	14.12

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.38 (br s, 8 H); 1.44 (s, 9 H); 2.6–2.7 (br s, 2 H); 3.2–5.0 (m, 2 H); 4.8–5.1 ppm (br s, 1 H).

Reaction of 1,7-Diamino-4-azaheptane (5) with 2:
To a solution of 1,7-diamino-4-azaheptane (**5**; 26.3 g, 0.2 mol) in dimethyl sulfoxide (125 ml) is added, dropwise, **2** (35.8 g, 0.25 mol) in ether (67 ml) while the temperature is kept at 25°C by cooling with Dry Ice/acetone. After the addition is completed (30 min), stirring is continued at room temperature for 1 h, whereupon water (250 ml) and ether (375 ml) are added. Under vigorous stirring, the reaction mixture is adjusted to pH 3 with 6 normal hydrochloric acid, after which the aqueous phase is extracted with ether (3 × 375 ml). The combined ether extracts are washed with water (2 × 100 ml), dried with anhydrous magnesium sulfate, and concentrated in vacuo to give crude **6** as a yellow oil; yield: 9.9 g (27% based on **2**, 12% based on **5**). No attempts were undertaken to purify this compound.

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.44 (s, 18 H); 1.47 (s, 9 H); 1.6–1.8 (m, 4 H); 3.1–3.3 (m, 8 H); 5.1–5.3 ppm (br s, 2 H).

The aqueous phases from above are combined, adjusted to pH 9.5 with 6 normal sodium hydroxide, and extracted with ether (4 × 350 ml). The combined ether extracts are dried with anhydrous magnesium sulfate, and concentrated in vacuo to give crude **7** as a semi-crystalline oil. The hydrochloride of **7** is prepared as described for **3b**; yield: 18.5 g (40% based on **2**, 25% based on **5**); m.p. 174–175°C (from ethyl acetate/hexane).

$C_{16}H_{33}N_3O_4 \cdot HCl$ (367.9)	calc.	C 52.24	H 9.32	N 11.42	Cl 9.64
	found	52.36	9.31	11.16	9.63

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.35 (br s, 1 H); 1.44 (s, 18 H); 1.6–1.8 (m, 4 H); 2.65 (t, 4 H, J = 6 Hz); 3.1–3.3 (m, 4 H); 5.3–5.5 ppm (br s, 2 H).

The remaining aqueous phase from above is concentrated to half its volume in vacuo, adjusted to pH 12 with 6 normal sodium hydroxide and extracted with ether (10 × 200 ml). Concentration of the ether phase in vacuo gives crude **8**, which is converted to its dihydrochloride as described for **3b**; yield: 15.9 g (21% based on **2**, 26% based on **5**); m.p. 203–204°C (from *n*-propanol).

$C_{11}H_{25}N_3O_2 \cdot 2HCl$ (304.3)	calc.	C 43.43	H 8.95	N 13.81	Cl 23.30
	found	43.26	9.15	13.79	23.40

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.3 (br s, 3 H); 1.43 (s, 9 H); 1.5–1.8 (m, 4 H); 2.6–2.8 (m, 6 H); 3.1–3.3 (m, 2 H); 5.6–5.8 ppm (br s, 1 H).

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[6] R. Andruszkiewicz et al., *Pol. J. Chem.* **52**, 1167 (1978) have described the synthesis of *N*-*t*-butyloxycarbonyl-1,4-diaminobutane but little analytical or spectroscopic data were provided.

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